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Binding and Response Selection in the Temporal Domain – a New Paradigm for Neurobiological Research

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Summary: Most cognitive functions are based on highly parallel and distributed information processing by the brain. A paradigmatic example is provided by the vertebrate visual system where numerous cortical areas have been described which analyse different types of visual information. At present, it is unclear how information can be integrated and how coherent representational states can be established in such distributed systems. We suggest that this so-called “binding problem” may be solved in the temporal domain. The hypothesis is that synchronization of neuronal discharges can serve for the integration of distributed neurons into coherent cell assemblies and that this process may underlie the selection of perceptually or behaviourally relevant information. In this paper, we review experimental results, mainly obtained in the visual system, which support this temporal binding hypothesis. In addition, we discuss the implications of this hypothesis as a heuristic for neurobiological research.

Introduction: the need for new research strategies

What does it mean, in neural terms, to see, to move, to communicate, or to be conscious of the world around us? How does our nervous system enable us to behave in such complex ways, and to do so effortlessly minute for minute of our lives? – These issues are among those which motivate neurobiological research and which continue to entangle scientists into the fascinating endeavour of studying animal and human brains. Still, we are far from being

able to answer these questions. During the past decades, neuroscientists have been highly successful in elucidating the constituents of neuronal networks at the cellular and molecular level. Detailed knowledge is now available about the morphological, physiological and biochemical features of neurons, and enormous efforts are being devoted to tracing their functional properties down to the level of individual molecules. However, despite the victorious career of this analytic approach we are still lacking an appropriate understanding of the brain's integrative functions: How do all the known components interact as a system, how can they develop synergy and be integrated into a functional whole? How do networks of neurons acquire those emergent functional properties that become evident in perception and behaviour? It is only recently that neurobiologists have seriously begun to address these issues. In part, this is due to the appearance of a new conceptual framework, which has overturned many of the traditional assumptions that used to pervade neurobiological thinking: the connectionist approach to the workings of brain and mind (Rumelhart et al., 1986; McClelland et al., 1986).

The key assumption of the connectionist approach is that any complex behaviour as well as *most cognitive functions* are based on the activity of large neuronal networks, rather than on small highly specialized patches of brain tissue that can, for a proper understanding of their function, be treated in isolation. As suggested by the large body of evidence available today, even low-level perceptual and memory tasks or the execution of simple movements require the activation of numerous brain regions and a massively parallel processing of information. Consequently, we have to assume that neural representations, i.e., those activity patterns in which the brain processes and stores information, are of a highly distributed nature. Understanding how large neuronal populations are coordinated for the formation of such representational states is one of the central goals of current neurobiological research: How can responses of individual neurons in the brain be integrated into organized patterns of activity which are functionally effective? Many researchers agree that resolving this issue, which is commonly addressed as the "binding problem", would constitute a major step towards understanding integrative processes in the nervous system (Crick, 1984; Sejnowski, 1986; Damasio, 1990; Treisman 1996).

Clearly, the connectionist approach has profound conceptual implications (for review see e.g. Rumelhart et al., 1986; Bechtel and Abrahamsen, 1991; Engel and König, 1997). In addition to shifting mainstream neurobiology from a localizationist stance to a strong belief in parallel and distributed processing, connectionism puts emphasis on the notions of self-organization and plasticity, these concepts becoming central to understanding not only the ontogenetic development of the brain but also its actual functioning during adulthood. Moreover, this approach inspires a much more holistic view on neuronal information processing by highlighting, for instance, the dependence of neuronal responses on behavioural or perceptual contexts

and their modulation by top-down influences such as attention or memory. Finally, the connectionist viewpoint strongly emphasizes the notion that cognitive systems are dynamic, i.e., their operating principles can only be captured if one considers their evolution in time. In addition to its outstanding conceptual importance, the connectionist shift from the single neuron level to population dynamics has methodological implications. There is wide agreement that studying distributed processing at the network and systems level requires new research strategies and new experimental tools (e.g. Aertsen et al., 1989; Gerstein et al., 1989; Palm 1990; Singer et al., 1997). Obviously, it becomes necessary to monitor large neuronal populations simultaneously rather than just one neuron at a time. In addition, experimental approaches are required which address the dynamics of neuronal interactions rather than merely the response properties of single cells. For these reasons, the classical methods for single unit recording have in recent years been complemented with multielectrode recording and imaging techniques. The development of these new techniques has, in turn, created a strong need for new concepts and methods in data analysis such as, for instance, algorithms that detect higher-order temporal patterns in multielectrode data sets (Abeles et al., 1993; Martignon et al., 1995). Moreover, the connectionist approach motivates new experimental strategies which do not optimize stimuli and training of animals for the search of one-to-one relations between isolated stimuli and neuronal responses but, rather, focus on tasks that require dynamic binding of distributed neuronal populations. In this paper, we will present a specific hypothesis concerning integration and response selection in distributed neuronal networks. This hypothesis predicts that time may be the key to solving the binding problem and that temporal binding mechanisms may be important for achieving functional coherence of distributed neuronal populations (Abeles, 1982; Abeles et al., 1993; von der Malsburg, 1981, 1995; Engel et al., 1992; Singer and Gray, 1995; Pöppel, 1997). For most of our discussion, we will consider one specific example for the issue of neural integration, namely, the problem of feature binding and perceptual representation in vision. Focussing on this system, experimental results obtained with multielectrode recording techniques will be reviewed, and some implications for sensory processing will be developed. In the final sections of this paper, we then put the concept of temporal binding into a wider perspective by considering data from other neural systems, and suggest its general relevance as a paradigm for understanding dynamic integration in distributed systems.

The binding problem: how is visual information integrated?

Visual perception clearly provides a paradigmatic case for studying the binding problem. Psychophysical studies have shown that the analysis of

visual scenes involves at least two crucial processing steps (Treisman, 1986, 1996). In a first step, specific features of objects such as, for instance, colour, motion or the orientation of contours, are detected by the visual system in a local and parallel manner. Subsequently, these perceptual components are integrated and bound into organized units to provide the basis for a coherent representation of the respective objects. As already shown by the studies of the Gestalt psychologists, this process of feature binding follows certain "Gestalt criteria" that include, for instance, the proximity or similarity of features (Köhler, 1930). This binding problem, as characterized in the psychophysical domain, has a correlate at the physiological level. From a neurobiological point of view, a mechanism for the functional coordination of large neuronal populations is required for several reasons. First, neurons in visual centers typically have spatially restricted receptive fields which – at least at early stages of processing – are small compared to the size of typical objects. Therefore, neuronal responses need to be bound within retinotopically mapped visual areas to represent the coherence of features across different parts of the visual field. Second, a given stimulus always activates a large number of neurons within a visual area and, thus, has a representation that is distributed over an extended population of feature-detecting cells. This principle of "coarse coding" (Rumelhart et al., 1986) makes a binding mechanism at the physiological level indispensable. Third, potential mechanisms for the integration of neural responses must also act over considerable distances to achieve binding across different visual areas. It is now commonly agreed upon that different classes of object features are processed in distinct cortical areas serving as "feature maps" (Felleman and Van Essen, 1991; Bullier and Nowak, 1995). In the monkey visual system, more than 30 visual areas have been characterized which can be grouped into different processing streams. In the cat, about 20 visual areas have been distinguished that differ considerably in the response properties of their neurons. Thus, neural activity must be integrated across the borders of individual areas to establish coherent representations of complex objects. Fourth, a versatile and highly flexible binding mechanism is required because, usually, multiple objects are present in the visual field all of which activate neurons in a large number of cortical areas. Thus, any mechanism supposed to solve the binding problem must be able to selectively "tag" feature-selective neurons that code for the same object and to demarcate their responses from those of neurons activated by other objects in order to avoid the illusory conjunction of features (von der Malsburg, 1981).

More than a decade ago it has been suggested that the binding problem might be solved by a temporal integration mechanism (von der Malsburg, 1981). According to this proposal, distributed cortical neurons could be bound into coherent assemblies by synchronization of their discharges with a precision in the range of few milliseconds (Fig. 1). This "temporal bind-

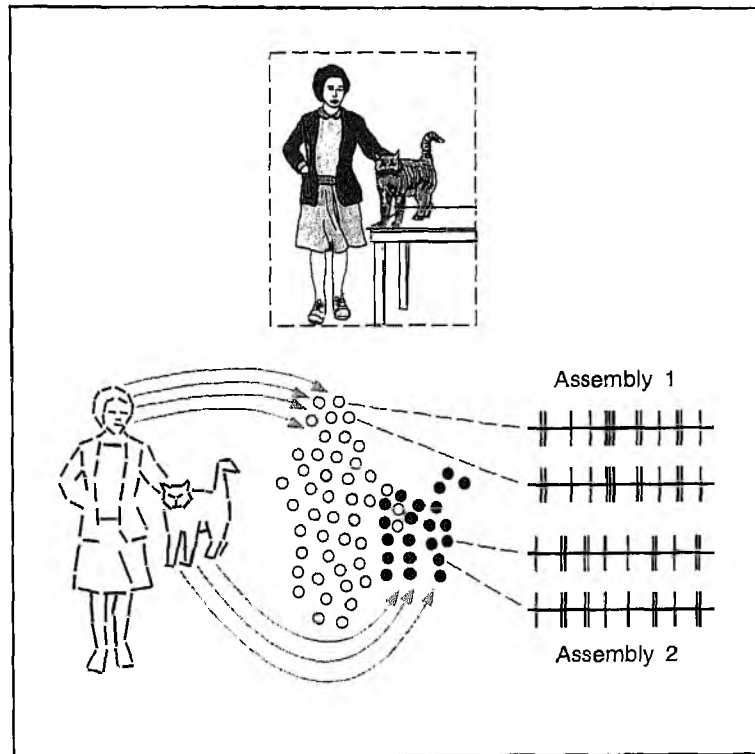


Fig. 1: Feature binding by synchronization. The temporal binding model assumes that objects are represented in the visual cortex by assemblies of synchronously firing neurons. In this example, the lady and her cat would each be represented by one such assembly (indicated by open and filled symbols, respectively). These assemblies comprise neurons which detect specific features of visual objects (such as, for instance, the orientation of contour segments) within their receptive fields (lower left). The relationship between the features can then be encoded by the temporal correlation among these neurons (lower right). The model assumes that neurons which are part of the same assembly fire in synchrony whereas no consistent temporal relation is found between cells belonging to different object representations.

ing model” predicts that perceptual coherence is reflected by the correlated firing of feature-sensitive neurons responding to the same visual object. In contrast, the discharges of cells responding to unrelated stimuli should not show such temporal correlation. The synchrony among neural discharges would provide an elegant way of “tagging” responses as being functionally related and of selecting these for further joint processing because synchrony can easily be detected by coincidence-sensitive neurons in other brain areas (Abeles, 1982; Singer and Gray, 1995; König et al., 1996). The absence of synchrony between different assemblies could then be exploited to achieve figure-ground segregation and segmentation of the visual scene (von der Malsburg, 1981, 1995).

This temporal binding mechanism seems attractive because it avoids pitfalls of more classical models. In a seminal paper, Barlow (1972) suggested that complex objects could be represented by the activity of very few or even individual neurons ("cardinal cells"). A severe shortcoming of this "single neuron doctrine" is that it leads to a combinatorial explosion with respect to the number of representational symbols needed (Sejnowski, 1986). According to this hypothesis, every new object eventually encountered will require the recruitment of new dedicated cells in the visual cortex. Therefore, the number of neurons required for an adequate representation of a realistic visual environment grows beyond any physiologically plausible estimate. The temporal binding model avoids this serious limitation because the same neurons can, in principle, be recombined into new representational patterns by merely changing the temporal relationships between their action potentials.

Furthermore, the temporal binding model complements and extends the classical notion of object representation by distributed neuronal assemblies (Hebb, 1949). The Hebb model implies that only one assembly is activated in a given area which "stands out" from a background of inactive cortical neurons and, thus, becomes salient as a representational unit for other brain areas. However, in natural visual scenes usually multiple objects are present which, in addition, can be embedded in a complex background. Thus, scene segmentation and figure-ground segregation are likely to require the concurrent representation of multiple sets of coherent inputs. However, coactivation of multiple Hebbian assemblies leads to unresolvable ambiguities. Because all neurons involved raise their average firing rate, specific relationships between subsets of responses cannot be defined in the overall activity pattern. In contrast, a crucial advantage of temporal binding is that several coactivated object representations remain distinguishable (von der Malsburg, 1981, 1995; Engel et al., 1992; Singer and Gray, 1995). As illustrated schematically in Fig. 1, the temporal relationship between neuronal discharges permits the unambiguous distinction of subsets of functionally related responses. Thus, the overall activity pattern is endowed with significant additional structure which can serve for the fast and reliable selection of visual responses for further processing.

Evidence for temporal binding in the visual system

Recent experimental work provides supportive evidence for this concept of a temporal binding mechanism. Using the approach of multielectrode recording and correlation analysis (Fig. 2), numerous studies have shown that neurons in both cortical and subcortical centers can synchronize their discharges with a precision in the millisecond range (for review, see Engel et al., 1992; Aertsen and Arndt, 1993; König and Engel, 1995; Singer and Gray, 1995). This has been demonstrated in particular for the visual sys-

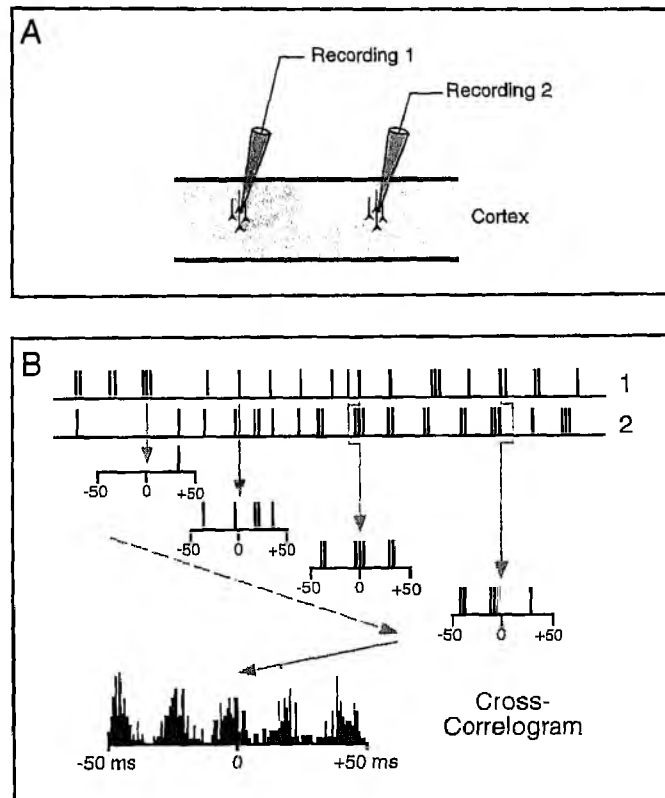


Fig. 2: Operation principle of correlation analysis. (A) To uncover neuronal synchrony, at least two electrodes are used to record from different sites simultaneously. (B) Correlation analysis can be applied to search for coincidences between the discharges recorded at sites 1 and 2. The algorithm counts incidents of precisely synchronized firing as well as the occurrence of discharges which lead or lag in phase relative to a reference spike in the first time series (in this case with phase shifts of up to ± 50 ms). Successive registration of these events yields the so-called crosscorrelogram. A central peak in the correlogram indicates synchronized neuronal firing. Eventually occurring side maxima reflect an oscillatory temporal modulation of the underlying neuronal responses (cf. Fig. 6).

tem, but similar observations have been made for the auditory, somatosensory and motor system, and related synchronization phenomena have also been found in cortical association areas.

In the cat visual system, several studies have demonstrated that spatially separate cells within individual visual areas can synchronize their spike discharges (Eckhorn et al., 1988; Gray et al., 1989; Engel et al., 1990; Brosch et al., 1995). Moreover, it has been shown that response synchronization can well extend beyond the borders of a single visual area. Thus, for instance, correlated firing has been observed between neurons located in different cerebral hemispheres (Engel et al., 1991a; Nowak et al., 1995). Figure 3

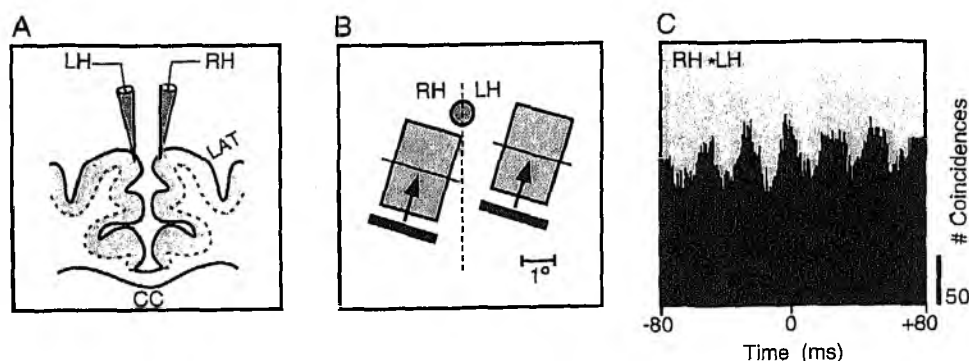


Fig. 3: Interhemispheric interactions in cat visual cortex. (A) In the anaesthetized animal electrodes were placed in the primary visual cortex of left and right hemisphere (LH, RH). LAT, lateral sulcus; CC, corpus callosum. (B) Plot of the receptive field locations for the two recording sites. The neurons had identical orientation preferences. The receptive fields were located in the respective contralateral hemifield in the vicinity of the vertical meridian (dashed line). The cells were activated with bar-shaped stimuli moved in the same direction across the receptive fields. The circle represents the center of the visual field. (C) Cross-correlogram computed for the recorded responses. The central maximum present in the correlogram indicates the coincident neuronal firing. The additional side maxima reflect an oscillatory temporal modulation of the neuronal responses (Modified from Engel et al., 1991a).

illustrates one of the measurements where this type of long-range interaction has been studied. In terms of the temporal binding hypothesis, this result is important because interhemispheric synchrony is required to bind the features of objects extending across the midline of the visual field. In addition, temporal correlations in cat visual cortex have been studied for neurons located in different areas of the same hemisphere (Eckhorn et al., 1988; Engel et al., 1991b; Nelson et al., 1992). Of particular interest is the finding that interactions can occur between areas with quite different response properties such as the primary visual cortex (area 17) and the posteromedial area in the lateral suprasylvian sulcus (PMLS), an extrastriate area involved in the processing of object motion (Engel et al., 1991b). As mentioned already, different areas are assumed to process different aspects of visual stimuli (Felleman and Van Essen, 1991; Bullier and Nowak, 1995) and, hence, interareal synchronization could mediate binding across feature maps which presumably is required for the complete representation of visual scenes. Finally, recent evidence shows that synchronous firing is not confined to the cortex but occurs already at the level of subcortical visual structures such as the retina, the lateral geniculate nucleus and the superior colliculus (Neuenschwander and Singer, 1996; Brecht and Engel, 1996). The majority of these studies on the cat visual system have been carried out in anesthetized preparations. However, the investigation of awake animals has yielded very similar results (Fries et al., 1996, 1997; Roelfsema et al., 1997).

A key finding in these studies on cat visual cortex is that response synchronization depends critically on the stimulus configuration. It could be demonstrated that spatially separate cells show strong synchronization only if they respond to the same visual object. However, if responding to two independent stimuli, the cells fire in a less correlated manner or even without any fixed temporal relationship. Figure 4 gives one example for this effect that has been observed both for the synchrony within (Gray et

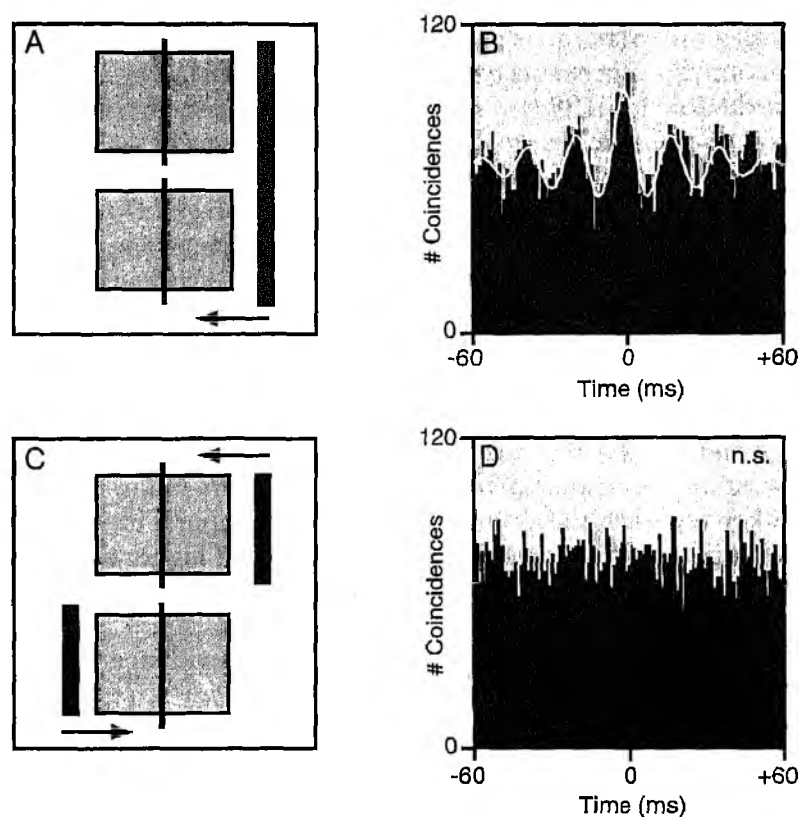


Fig. 4: Stimulus-dependence of long-range synchronization in the visual cortex. Data are from an experiment in which neuronal responses were recorded from two sites separated by 7 mm in the primary visual cortex of an anaesthetized cat. (A, C) Schematic plots of the receptive fields. At both recording sites the cells preferred vertical orientations. The colinear arrangement of the fields allowed the comparison of different stimulus paradigms. The neurons were activated with either a long continuous light bar moving across both fields (A) or two light bars moving in opposite directions (C). (B, D) The respective crosscorrelograms obtained with each stimulus paradigm. Using the long light bar, the two responses were synchronized as indicated by the strong modulation of the correlogram (B). Synchrony disappeared with the two incoherently moving stimuli (D); n.s., not significant. The graph superimposed to the correlogram in (B) represents a damped cosine function that was fitted to the data to assess the strength of the modulation. (Modified from Engel et al., 1992).

al., 1989; Engel et al., 1991c; Freiwald et al., 1995) as well as across visual areas (Engel et al., 1991b). The experiments demonstrate that Gestalt criteria such as continuity or coherent motion, which have psychophysically been shown to determine scene segmentation, are important for the establishment of synchrony among neurons in the visual cortex. These data provide strong support for the hypothesis that correlated firing could provide a dynamic mechanism which permits binding and response selection in a flexible manner.

Studies performed in the visual system of other species suggest that the results obtained in the cat may be generalized. Neuronal synchronization with similar characteristics has been observed in the visual system of non-mammalian species as different as pigeon (Neuenschwander et al., 1996) or turtle (Prechtl, 1994). Of particular relevance is, of course, the demonstration of comparable synchronization phenomena in the visual system of primates. In monkeys, precise synchronization of spatially separate neurons has been demonstrated both within striate and extrastriate cortex (Ts'o and Gilbert, 1988; Kreiter and Singer, 1992; Livingstone, 1996). In addition, correlated firing has been reported to occur between neurons of different visual areas (Frien et al., 1994; Salin and Bullier, 1995). Moreover, the stimulus-dependence of neuronal interactions has recently been confirmed in awake monkeys (Kreiter and Singer, 1996). Finally, EEG studies have provided similar evidence for precise synchronization in human visual cortex and suggest that the synchrony is relevant for the perception of coherent stimulus arrangements (Tallon et al., 1995; Tallon-Baudry et al., 1996). Taken together, these studies suggest that temporal binding might be a general operating principle in the visual system of higher vertebrates.

Functional relevance of synchronization: evidence from strabismic subjects

Although the temporal binding model offers an attractive conceptual scheme for understanding the integration of distributed neuronal responses, definitive evidence that the brain actually uses synchronization in exactly this way has not yet been obtained. The first hint that neuronal synchronization is indeed functionally relevant and related to the animal's perception was provided by experiments on cats with divergent squint (König et al., 1993). Typically, humans and animals with a divergent strabismus develop a pattern of alternating fixation with the two eyes. Usually, monocular vision is undisturbed in these subjects, but they show a striking inability of combining information into a single percept that arrives simultaneously through the two eyes. In animals with this malfunction, the perceptual deficit is accompanied by a loss of synchronization between neurons that receive information from different eyes (König et al., 1993). This

correspondence between a functional deficit and loss of neuronal interaction argues for the importance of correlated neuronal firing in normal visual perception.

Further evidence for the functional relevance of synchrony among cortical neurons comes from a more recent correlation study of cats with convergent squint (Roelfsema et al., 1994a). Unlike subjects with a divergent strabismus, convergent squinters often use only one eye for fixation. The non-fixating eye then develops a syndrome of perceptual deficits called strabismic amblyopia. Symptoms of strabismic amblyopia include a reduced acuity of the affected eye, temporal instability and spatial distortions of the visual image, and the so-called crowding phenomenon, i.e., discrimination of details deteriorates further if other contours are nearby. Clearly, at least some of these deficits indicate a reduced capacity of integrating visual information and an impairment of the mechanisms responsible for feature bind-

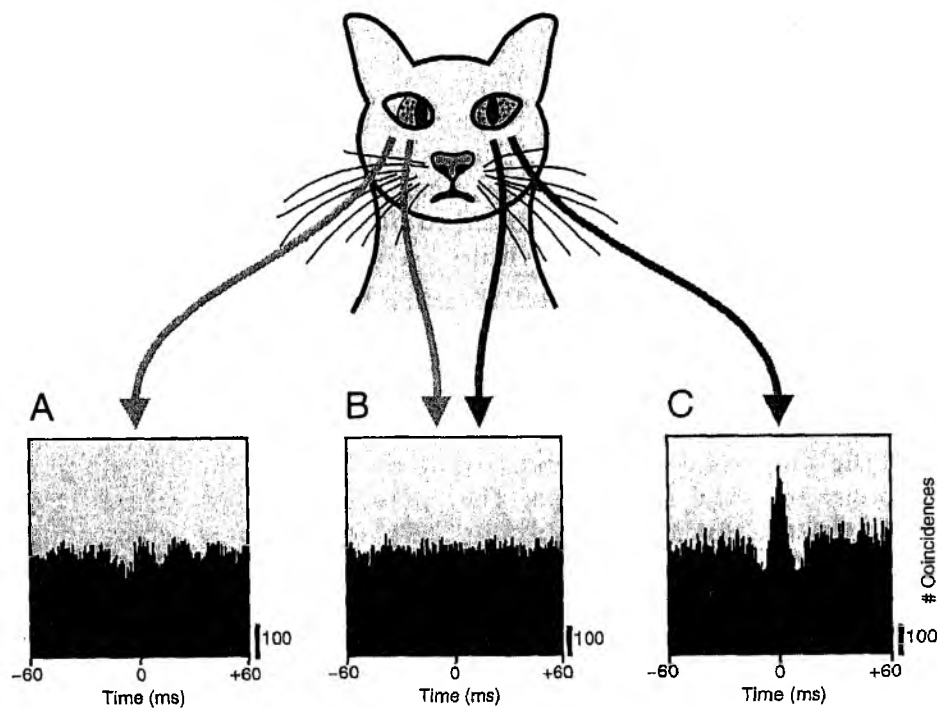


Fig. 5: Neuronal synchronization in the primary visual cortex of cats with strabismic amblyopia. The lower panel shows examples of crosscorrelograms between cells driven by the normal eye, by the amblyopic eye and between cells dominated by different eyes. Temporal correlation is strong if both recording sites are driven by the normal eye (C). Synchronization is, on average, much weaker between cells dominated by the amblyopic eye (A) and is in most cases negligible if the recording sites receive their input from different eyes (B). (Modified from Roelfsema et al., 1994a).

ing. The results of the correlation study by Roelfsema et al. (1994a) indicate that these perceptual deficits may be due to a disturbance of intracortical interactions. As illustrated in Fig. 5, clear differences can be observed in the synchronization of cells driven by the normal and the amblyopic eye, respectively. Visually evoked responses recorded from neurons dominated by the amblyopic eye showed a much weaker correlation than the discharges of neurons driven by the normal eye. In addition, synchronization between neurons dominated by different eyes was virtually absent, confirming the results that had been obtained in cats with divergent squint (König et al., 1993). However, in terms of average firing rates the responses were very similar for neurons driven by the normal and amblyopic eye. These results indicate that strabismic amblyopia is accompanied by a selective impairment of intracortical interactions. Indirectly, this result corroborates the idea that neuronal synchrony is indeed employed for feature integration and, hence, an important variable for cortical information processing.

Even more direct evidence for a relation between neural synchronization and perception comes from recent experiments in which neuronal responses were recorded from the visual cortex of strabismic cats under conditions of binocular rivalry (Fries et al., 1996, 1997). In contrast to the two studies mentioned above, these measurements were performed in awake animals with chronically implanted wire electrodes. The animals were subjected to dichoptic visual stimulation, i.e. different moving patterns were simultaneously presented to the left and the right eye, respectively. Under these conditions, rivalry occurs between the two stimuli and, thus, only one eye contributes to perception at a given moment (the dominant eye) whereas the information arriving through the other eye (the suppressed eye) is excluded from perceptual experience and behavioural control. The experiments carried out with this experimental paradigm (Fries et al., 1996, 1997) show that visual cortical neurons driven by the dominant and the suppressed eye, respectively, do not differ in the strength of their response to visual stimulation. They show, however, striking differences with respect to their synchronization behaviour. Neurons representing the perceptually dominant stimulus increase their synchrony, whereas cells processing the suppressed visual pattern decrease their temporal correlation. These data provide direct support for the hypothesis that temporal structure in neural activity patterns is related to the formation of percepts and that enhanced synchrony in neuronal populations may contribute to the selection of perceptually and behaviourally relevant information.

Potential significance of oscillatory firing patterns

A striking observation made in many of the correlation studies described above is that the emergence of synchronized states in the cortex is fre-

quently associated with oscillatory firing patterns of the respective neurons (Eckhorn et al., 1988; Gray et al., 1989; Engel et al., 1990, 1991a, 1991b, 1991c; Kreiter and Singer, 1992; König et al., 1993; Fries et al., 1994; Roelfsema et al., 1994a; Brosch et al., 1995; König et al., 1995; Freiwald et al., 1995; Neuenschwander et al., 1996; Neuenschwander and Singer, 1996; Kreiter and Singer, 1996; Brecht and Engel, 1996; Livingstone, 1996; Gray and McCormick, 1996; Fries et al., 1996, 1997). These temporal patterns, which induce troughs and additional peaks in correlograms (Figs. 3, 4), were first described in the visual system by Gray and Singer (1989). They observed that, with appropriate stimulation, neighbouring neurons tend to engage in grouped discharges which recur at frequencies in the gamma range between 30 and 80 Hz (Fig. 6).

In the preceding sections, we have argued that synchronous firing may serve for the dynamic binding and selection of distributed neuronal responses. This, then, raises the question of what role the oscillatory firing patterns might play as part of such a temporal binding mechanism. One possible answer is suggested by simulation studies that have investigated the interactions of coupled neuronal elements (König and Schillen, 1991). The results of these studies indicate that an oscillatory modulation of neuronal responses may have crucial advantages for the establishment of precise synchrony between widely remote sites in the cortex and, thus, may be instrumental as a “carrier signal” for temporal binding in the brain (Engel et al., 1992, König et al., 1995). Recent evidence shows that response syn-

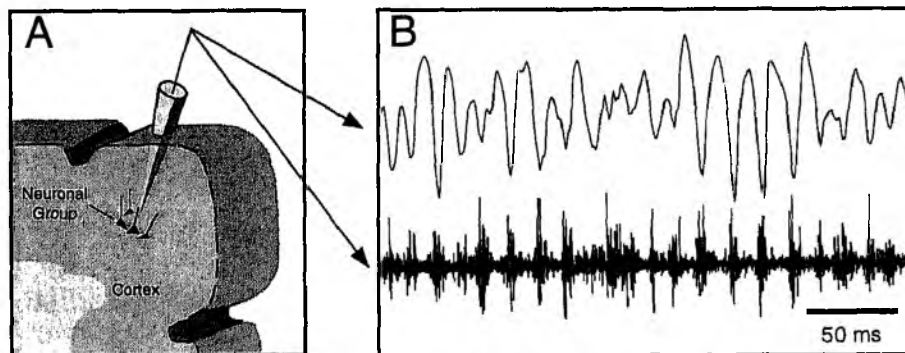


Fig. 6: Example of an oscillatory response in cat primary visual cortex. (A) In this experiment, the activity of a small group of neurons was recorded by means of a low-impedance electrode. (B) By filtering in different bandpasses, a local field potential (top, positivity upward) and multiunit spike activity (bottom) can be extracted from the raw electrode signal. As a light bar is passed through the cells' receptive field a clear oscillatory response is observed in the field potential, indicating that the neurons of the recorded cluster have engaged in a coherent and rhythmic firing pattern. Note the variability of both amplitude and frequency. The multiunit recording shows directly that different neurons (as indicated by spikes of different sizes) synchronize their discharges into a burst-and-pause firing pattern. Note that the spike bursts are in phase with the peak negativity of the field potential. (Modified from Roelfsema et al., 1994b).

chronization is mediated by connections at the cortical level and not by synchronously driving subcortical input (Engel et al., 1991a; Munk et al., 1995; König et al., 1993). Interestingly, interareal and interhemispheric interactions have consistently been observed to occur with near-zero phase lag (Engel et al., 1991a, 1991b; Nelson et al., 1992; Fries et al., 1994; Roelfsema et al., 1997; cf. Fig. 3), although the underlying cortico-cortical connections are known to exhibit considerable transmission delays. As suggested by the simulation studies, the establishment of synchrony without phase lag may be facilitated under these conditions if the respective neu-

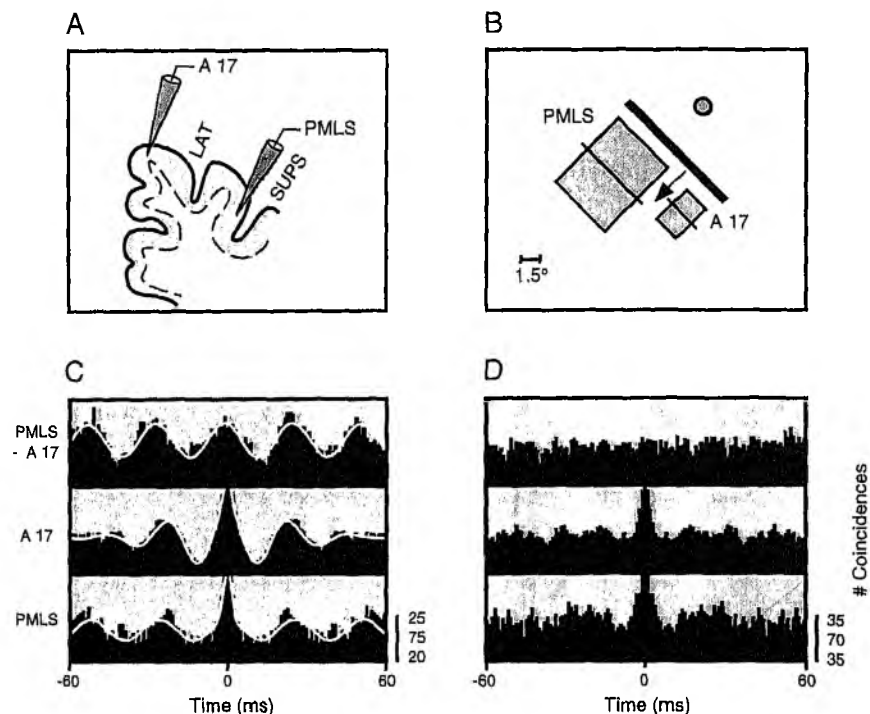


Fig. 7: Long-range synchronization is accompanied by oscillatory firing patterns. (A) Data are from an experiment in which one of the recording sites was located in the primary visual cortex (A 17), the other in extrastriate area PMLS. LAT, lateral sulcus; SUPS, suprasylvian sulcus. (B) The cells at the two recording sites had nonoverlapping receptive fields but their response properties were sufficiently similar to allow for coactivation with a single moving stimulus. In this case, a large number of trials were recorded using the same stimulus. Figures C and D show data from two representative response epochs. (C) Example of a trial where both cell groups showed narrow-banded oscillations, as indicated by the presence of multiple peaks and troughs in the autocorrelograms (middle and bottom). This is reflected in a strong modulation of the corresponding crosscorrelogram (top). (D) Example of a sweep where no temporal correlation was evident in the crosscorrelation function (top). The two autocorrelograms (middle and bottom) showed only a center peak without significant satellite peaks. As in Fig. 4, the continuous line superimposed on some of the correlograms represents a damped cosine function fitted to the data. (Modified from Roelfsema et al., 1994b).

rons show oscillatory firing patterns (König and Schillen, 1991). These models demonstrate that due to the recurrent temporal structure of such patterns reciprocally coupled neurons can entrain each other and improve synchrony within a few oscillatory bursts. Further advantages of oscillatory activity suggested by these models are that oscillating neurons can be synchronized via polysynaptic linkages without adding up of small phase-lags and that synchrony in such networks is robust despite considerable spatial variation of the conduction delays.

If the predictions suggested by these modelling studies hold true, cortical long-range synchronization should be closely correlated with the occurrence of oscillatory activity. However, such a relation would not necessarily hold for synchrony between closely spaced cells, since these tend to be strongly coupled without major delays in the respective connections. Recently, physiological evidence has been obtained in support of this hypothesis (König et al., 1995). Indeed, the physiological data demonstrate a close relationship between long-range synchronization and oscillatory firing patterns. If synchronization occurs over large distances within striate cortex, between areas or across the hemispheres it is almost always accompanied by oscillatory response patterns (Fig. 7). In contrast, short-range interactions can occur both with and without oscillatory modulation of the responses. These data support the hypothesis that oscillatory firing patterns may facilitate the establishment of precise synchrony between widely separate neuronal populations in the brain (Engel et al., 1992; König et al., 1995). If so, these discharge patterns may actually be a prerequisite for the binding of distributed neurons into assemblies and for the buildup of coherent representational states. Clearly, however, the role of oscillatory firing patterns needs to be substantiated by further experiments. Based on the available data, the possibility cannot be ruled out that synchrony is achieved by mechanisms which do not strictly require a band-limited temporal structure of neuronal responses.

Visual information processing: implications of temporal binding

The key assumption of the temporal binding model is that time constitutes an important variable for neural information processing. The evidence reviewed above suggests that synchrony is not a mere epiphenomenon of cortical circuitry as assumed in classical cross-correlation analysis but, rather, reflects a dynamic functional coupling which is causally relevant in the system. By making time available as an additional coding dimension, the binding mechanism suggested by von der Malsburg allows to express specific relationships and, thus, to endow neuronal activity patterns with a rich internal structure. In the current debate about the implementation of representational states in connectionist models (Rumelhart et al., 1986) it

has been argued that a combinatorial or “syntactic” structure of internal states is required to encode complex objects and to represent conjunctions of facts or events in the network (Fodor and Pylyshyn, 1988). This problem can be settled by temporal binding because appropriate synchronization can establish specific relations among the constituents of neural representations. This is not possible if average firing rates or activation levels serve as the only coding dimension (von der Malsburg, 1981, 1995; Fodor and Pylyshyn, 1988).

As described earlier in this paper, sensory information processing is assumed to be massively parallel and distributed (Rumelhart et al., 1986; McClelland et al., 1986; Felleman and Van Essen, 1991; Bullier and Nowak, 1995). For a number of reasons, the temporal binding model agrees well with this view on the architecture of sensory systems: Temporal binding permits the integration of sensory information without anatomical convergence of different processing streams (Felleman und Van Essen, 1991) to a single visual “master area”. Furthermore, synchronization can implement parallel interactions between visual neurons and cells located in other cortical or subcortical systems. Finally, the notion of parallel processing is in accord with the idea that representations are not instantiated by localized symbols (“cardinal cells”) but by temporally defined assemblies extending across cortical areas.

However, several implications of the temporal binding model seem in conflict with still prevailing intuitions about sensory processing. For instance, the hypothesis advocated here implies a firmly holistic view on the architecture of the visual system. The representational code implemented by synchrony is strictly relational: the activity of individual neurons – considered in isolation – has a rather limited causal efficacy, because the functional significance of a neuron depends on the context set by the other members of the assembly. In this sense, processing has “gestalt-quality”. This holistic stance, which converges with classical gestalt psychological notions (Köhler, 1930), is incompatible with the atomistic framework that emphasizes the single neuron as the relevant level of description (Barlow, 1972) – a view still pervading much of neurobiological thinking.

Moreover, the temporal binding model conflicts with the now-classical assumption that the visual cortex is characterized by a serial-hierarchical structure comprising independent processing pathways (Felleman und Van Essen, 1991). With respect to the cat visual system, the findings on inter-areal interactions reviewed above suggest that neurons in different processing pathways are by no means independently active but, rather, can be tied into the same assembly (Eckhorn et al., 1988; Engel et al., 1991b; Nelson et al., 1992). For the primate visual system we are still lacking the experimental proof of synchrony between areas that are part of different processing pathways. However, the temporal binding model predicts that also in primates synchrony should be observed across processing streams (in

accordance with known anatomical cross-talk) which would serve for the binding of different classes of features. Interestingly, temporal correlations have recently been found between monkey primary (V1) and secondary (V2) visual cortex (Frien et al., 1994; Salin and Bullier, 1995). As in the case of intra-areal interactions, synchrony between these two areas occurs, on average, with zero phase lag. This finding suggests a parallel activation of V1 and V2 neurons rather than a serial-hierarchical transfer of information and, therefore, contradicts the standard assumption that these two areas represent different levels in the presumed hierarchy of visual areas (Felleman and Van Essen, 1991). This conclusion is supported by a number of additional anatomical and physiological findings (for review, see Bullier and Nowak, 1995).

Finally, it seems worth emphasizing that the temporal binding model is compatible with the idea that “top-down” influences play an important role for scene segmentation and figure-ground segregation (Treisman, 1986) – which does not necessarily hold for more classical models of visual segmentation such as, for instance, the theoretical approach by Marr (1982). In a recent study (Munk et al., 1996) it could be shown that stimulus-induced synchrony in visual cortex is not fully determined by the peripheral stimulus and by the binding criteria implemented in the architecture of the respective visual area. Rather, the experiments demonstrate a profound influence of central modulatory systems which participate in the control of arousal and attention. Similarly, recent measurements in awake behaving cats show that temporal correlation between cortical cell populations critically depends on the behavioural situation the animal is engaged in (Roelfsema et al., 1997).

Synchrony as a general mechanism for integration and response selection

In this paper, we have reviewed experimental evidence suggesting the existence of a temporal binding mechanism. The available data support the hypothesis that correlated firing may be functionally relevant in the brain for the binding of distributed neurons into coherently active assemblies and the dynamic selection of their responses for joint processing. Moreover, the results suggest that oscillatory firing patterns with frequencies in the gamma range may play a crucial role as carrier signals for the establishment of synchrony. So far, we have restricted our discussion to evidence obtained in the visual system. However, it seems likely that binding problems similar to those observed in vision are faced in other functional systems as well. The problem of visual feature integration just exemplifies a much more general problem of integration that always occurs in neuronal networks operating on the basis of “coarse coding” and distributed repre-

coordination task (Fig. 8; Roelfsema et al., 1997). In these animals, local field potentials were recorded with electrodes chronically implanted in various areas of the visual, parietal and motor cortex. The results of this study show that synchronization of neural responses does not only occur within the visual system, but also between visual and parietal areas as well as between parietal and motor cortex (Fig. 8). Moreover, the interareal interactions changed dramatically in different behavioural situations. Both findings suggest that synchrony may indeed be relevant for visuomotor coordination and may serve for the linkage of sensory and motor aspects of behaviour. The specificity of such interactions might allow, for instance, the selective channeling of sensory information to different motor programs which are concurrently executed (Roelfsema et al., 1996). We assume that further studies of the synchronization between sensory cortices and the motor system may lead to valuable insights into how temporally coded sensory information might be used for suitable behavioural adjustments.

Directions for future research

Taken together, the available studies suggest that comparable synchronization phenomena are found in a large number of different functional systems. Thus, it seems justified to generalize the results obtained in the visual cortex and to suggest that temporal binding may be of general relevance for neural information processing. Importantly, these studies provide increasing evidence that temporal binding, in particular at frequencies in the gamma band, may also occur in the human brain. Yet, it must be kept in mind that for most of the functional systems considered in the preceding section the available data demonstrate merely the presence of correlated neural activity. To prove that these temporal correlations do indeed serve for binding and response selection, additional data must be provided showing that the synchrony can be influenced by changes in stimulus configurations or by alterations of the behavioural context (e.g. Vaadia et al., 1995). At this point, the studies of the visual system seem to provide the most convincing evidence for the existence of temporal binding mechanisms. Yet, even here additional studies are required to further corroborate the causal relevance of temporal structure for perception.

Furthermore, important questions regarding the representational power of temporally coded assemblies are unresolved. As introduced here, the concept of temporal coding *prima facie* refers only to the representation of the image of currently visible objects. What remains to be shown is how, in addition, abstract schemata or prototypes of objects can be encoded by using synchronized assemblies. Moreover, it is unclear how representational states can be constructed in a hierarchical manner by exploiting the temporal structure in neural activity patterns. This might be needed, for instance,

to encode the coherence of features that make up individual parts of an object plus the relations between those parts. Moreover, this may be indispensable to represent the relations between different objects in complex visual scenes. Finally, it seems interesting to ask what role precise temporal correlations might play for the representation of sequences of events (like encoding a melody or a spoken sentence) and for the generation of sequential output (like the succession of motor commands during movements).

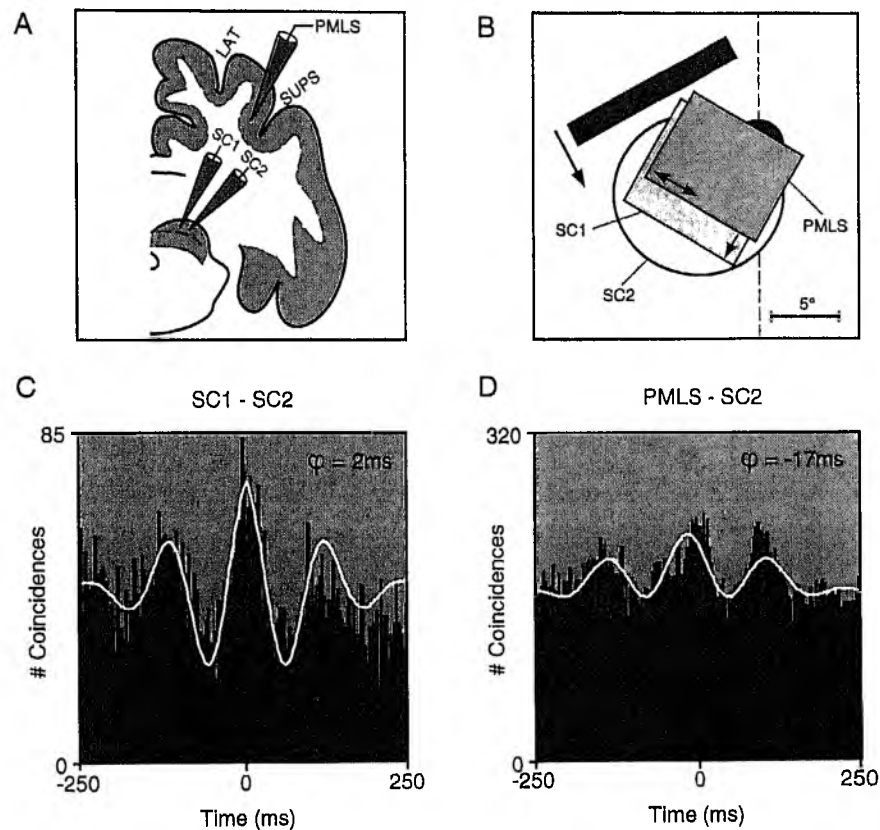


Fig. 9: Corticotectal interactions in the cat. (A) Data are from a measurement where simultaneous recordings were made from two sites in the superior colliculus (SC1, SC2) and the extrastriate area PMLS. LAT, lateral sulcus; SUPS, suprasylvian sulcus. (B) Schematic plot of the receptive fields for all three recording sites. All fields were overlapping and, hence, the cells were activated with a single moving light bar. (C) Crosscorrelogram for the interaction between the two tectal cell groups. Note that the interaction occurs at a frequency in the alpha range (around 10 Hz) and with only a small phase shift (ϕ). (D) Crosscorrelogram for the responses obtained at SC2 and at the PMLS recording site. The correlation occurs in a similar frequency band, but shows a pronounced phase shift of about 17 ms indicating that the PMLS cells were firing earlier than the collicular units. The continuous line superimposed on the correlograms represents the generalized Gabor function that was fitted to the data. (From Brecht and Engel, 1996).

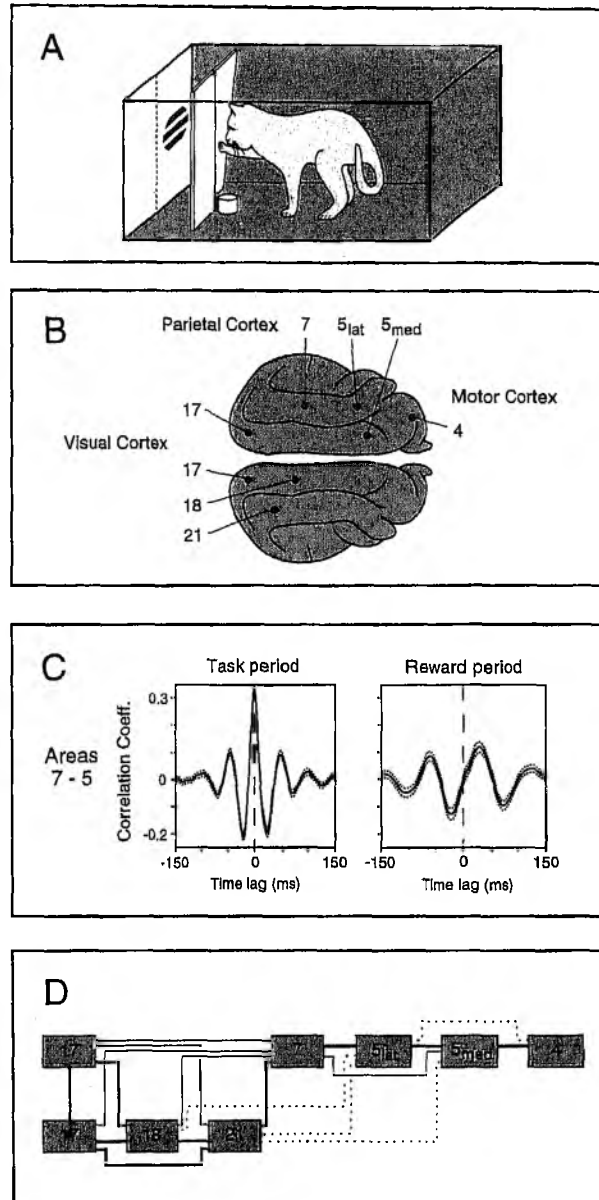
sentation (Sejnowski, 1986; Damasio, 1990). Since information processing in other sensory modalities and in the motor system is also highly parallel, the needs to organize and bind distributed responses are similar to the visual system. Furthermore, information must be flexibly coordinated both across sensory modalities as well as between sensory and motor processes in order to allow for adaptive behaviour of the organism. The hypothesis pursued here predicts, therefore, that temporal binding mechanisms should exist in other cortical systems and, moreover, that synchrony should occur between different systems.

Indeed, several recent findings suggest that the temporal binding model can be generalized to other functional neural systems. Studies in non-visual sensory modalities and in the motor system indicate that synchrony and oscillatory activity may actually be quite ubiquitous in the nervous system. Synchronization with prevalence of the gamma frequency range is well known to occur in the olfactory system of various vertebrate and invertebrate species, where these phenomena have been related to the processing of odor information (Freeman, 1988; Laurent, 1996). In the auditory cortex, synchronized gamma oscillations have been described by several groups. In humans, these phenomena have been observed with EEG and MEG (magneto-encephalographic) techniques (Galambos et al., 1981; Pantev et al., 1991; Madler et al., 1991). In addition, temporal correlations in auditory cortex have been observed in animal experiments (Eggermont, 1992; deCharms and Merzenich, 1996). In the somatosensory system, interactions in this frequency range have recently been described in the awake monkey (Murthy and Fetz, 1992). Furthermore, synchronized oscillatory firing has been observed in other systems like the hippocampus (Bragin et al., 1995; Buzsáki and Chrobak, 1995).

Similar evidence is available for the motor system where neural synchronization in the gamma frequency range has been discovered in monkeys (Murthy and Fetz, 1992; Sanes and Donoghue, 1993) and in humans (Kristeva-Feige et al., 1993). It seems interesting to relate these findings to the dynamics of so-called central pattern generators, i.e., networks of coupled oscillators found in the spinal cord of vertebrates and in the nervous system of invertebrates which are involved in the execution of basic motor programs (Grillner et al., 1991). Although the frequency of rhythmic activity is far below the gamma range in these systems, the principles of pattern generation appear similar. The same sets of neurons can be used to generate a large diversity of different patterns by changing the coupling strength among oscillatory modules and by modulating oscillation frequencies.

Remarkably, there is evidence to suggest that synchrony may also play a role for sensorimotor integration. In monkeys, synchronization between sensory and motor cortical areas has been reported (Murthy and Fetz, 1992; Bressler et al., 1993). Similar results have been obtained in a recent study on awake behaving cats that were trained to perform a visuomotor

Fig. 8: Synchronization between visual, parietal and motor cortex in awake behaving cats. Local field potentials were recorded with electrodes chronically implanted in several areas of the visual and parietal cortex as well as in the primary motor cortex. (A) The cats were situated unrestrained in a testing box and had to watch a screen through a transparent door. At the beginning of each trial, a grating was projected onto the screen. The cat had to respond by pressing the door with the forepaw and had to hold it until the grating was rotated. Upon change of the visual stimulus, the animal had to release the door. After correct trials, a reward was presented in a food well at the bottom of the box. (B) Location of the recording sites. Electrodes were implanted in areas 17, 18 and 21 of the visual cortex, in areas 5 and 7 of parietal cortex and in area 4 of the motor cortex where the forepaw is represented that the cat used for pressing the door. (C) Example of synchronization between areas 7 and 5 of the parietal cortex during the task period, i.e. the epoch where the cat was watching the grating and waiting for its rotation (left) and the reward period (right). The interactions are dependent on the behavioural context. Thus, during the task, zero-phase synchrony occurs between the areas. However, during the reward period the synchrony is lost and a large phase-shift appears in the correlogram. (D) Summary of temporal correlation between the recorded areas during the task period. Thick lines indicate strong correlation (correlation coefficients larger than 0.10), thin and hatched lines show weak, but still significant interactions (correlation coefficients smaller than 0.10 or smaller than 0.05, respectively). Areas have been placed according to their position in the processing stream that links the visual cortex to the motor cortex. The diagram shows that precise synchrony is a global cortical phenomenon and is not restricted to the visual cortex. (Modified from Roelfsema et al., 1997).



Another unresolved problem that has not been addressed experimentally so far concerns the issue of “readout” of temporal patterns. Obviously, temporally coded information somehow needs to be transformed into behavioural responses. This poses the question of how the premotor and motor cortex or subcortical integrative structures such as, for instance, the superior colliculus, can utilize information carried by assemblies of synchronized neurons. The available data on synchronization between sensory and motor cortical areas (Murthy and Fetz, 1992; Bressler et al., 1993; Roelfsema et al., 1997) do indeed suggest the possibility of a “readout” by motor systems. However, the detailed mechanisms of sensori-motor transfer of temporal information still need to be worked out. The possibility of “readout” by the superior colliculus is indicated by the fact that neurons in visual cortical areas can also synchronize, via the corticotectal pathway, with cells in the superficial layers of the colliculus (Brecht and Engel, 1996). An example for these corticotectal interactions is illustrated in Figure 9. Here, further studies are on the way to clarify the role of temporal patterns for the selection of targets during orienting responses of the animal, which are mediated by the superior colliculus (Brecht et al., 1997). Resolving this issue of “readout” will also require more detailed studies of the conditions under which neurons in these systems can act as coincidence detectors and of the biophysical properties that enable such cells to selectively respond to inputs showing precise correlation in the range of only few milliseconds (König et al., 1996).

Clearly, the most enigmatic issue is whether the concept of temporally coded representations can possibly contribute to a neurobiological theory of phenomenal consciousness, i.e., to a theory describing the neuronal correlates of subjective experience and the necessary (and possibly sufficient) conditions for the occurrence of qualia (for a review on the current debate of this issue, see Metzinger, 1995). As described above, there is now at least preliminary evidence that synchronized neuronal firing may be required for the buildup of percepts (Fries et al., 1996, 1997). If true, this would indicate that appropriate binding of neural responses participating in a representational state could be a necessary condition to grant access of this information to phenomenal consciousness. Certainly, further investigation of this hypothesis will require experiments on humans in which the relation between the fast dynamics of neural activity and phenomenal states can be studied by EEG and MEG techniques.

Concluding remarks

In summary, we suggest that the concept of temporal binding may provide a useful paradigm for approaching the problems of integration and response selection in distributed neuronal networks. This concept differs criti-

cally from more classical models that invoke "cardinal cells" (Barlow, 1972) or specialized "binding units" (Rumelhart et al., 1986) because it introduces synchrony as an additional coding dimension which complements the conventional rate code. While the latter serves for the coarse coding of representational contents, the former permits the dynamic expression of specific relations within the network. In this way, the combination of two different coding strategies allows the multiplexing of different types of information within the same activity patterns and, thus, enhances the representational power of distributed systems. As discussed above, this concept has primed a search for assemblies and for stimulus- and task-dependent temporal correlations in the visual system, which has already yielded substantial evidence supporting the notion of temporal binding. A growing body of data indicates that similar mechanisms may operate in other neural systems as well. This suggests that the concept of temporal binding, as developed with respect to visual processing, may provide a fertile heuristic for research in other areas of neurobiology.

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